



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	09/806,125	Art Unit:	1642
Filed:	March 28, 2001	Examiner:	S. Rawlings
1 st Inventor:	E. Matsutani	Allowed:	
For:	Agent That Retards Transformation of Hormone-Dependent Cancer to Non- Hormone Dependent Cancer	Batch:	
Atty. Dkt. No.	2556 USOP	Paper No.:	

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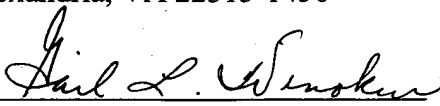
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Gail L. Winokur

Takeda Pharmaceuticals North America, Inc.
Intellectual Property Department
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1642 IFW

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	Filing Date	March 28, 2001	
	First Named Inventor	E. Matsutani	
	Art Unit	1642	
	Examiner Name	S. Rawlings	
Total Number of Pages in This Submission	6	Attorney Docket Number	2556 USOP

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

E. MATSUTANI et al

Examiner: Stephen L. Rawlings, Ph.D.

Serial No. 09/806,125

Group Art Unit: 1642

Filed on March 28, 2001

For Agent That Retards Transformation of Hormone-Dependent
Cancer to Non-Hormone-Dependent Cancer

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of
Patents and Trademarks,
P.O. Box 1450
Arlington, VA 22313-1450

Sir:

I, Mr. Kenichiro Naito, a citizen of Japan, and residing at 11-17, Segawa
2-chome, Minoh-shi, Osaka, 562-0045 JAPAN sincerely declare:

That I was born on June 30, 1958 in Ukyo-ku, Kyoto, Japan and graduated
from the medical school, Osaka University, Japan, in March 1984;

That I have been employed by Takeda Pharmaceutical Company Limited,
Osaka, Japan since April 1984, and have been engaged in pharmacological
research at the Biology Research Laboratories of the Pharmaceutical Research
Division of Takeda since 1984;

That I am a member of the Japanese cancer association, the molecular
biology society of Japan and the Japanese society of hematology.

That I am one of the co-inventors of United States Patent Application Serial
No. 09/806,125 filed 3/28/2001.

That under my direction and/or control, the following experiments were
conducted:

Experimental Procedure

Cells of the human prostatic cancer cell line LNCaP in passage culture were trypsinized and suspended in RPMI1640 medium (Gibco BRL) containing 10% fetal bovine serum (BioWhittaker). The cell density of this cell suspension was determined using a CDA-500(Sysmex)and adjusted to 2×10^4 cells/ml using the medium described above. This suspension was dispensed to a 24-well multi-well culture plate (Becton Dickinson) at 0.5 ml per well and cultured at 37°C in the presence of 5% CO₂ overnight.

To each well,

- (i) 0.5 ml of a medium containing a preset concentration of 1×10^{-5} M cyproterone acetate (Sigma; Cat. No. C-3412),
- (ii) 0.5 ml of a medium containing a preset concentration of cyproterone acetate and 0.4μ M AG17 (Terada, H. 1981. Biochem. Biophys. Acta 639, 225),
- (iii) 0.5 ml of a medium containing a preset concentration of cyproterone acetate and 20μ M AG1024 (Ohmichi, M., et al. 1993. Biochemistry 32, 4650),
- (iv) 0.5 ml of a medium containing a preset concentration of cyproterone acetate and 20μ M AG1296 (Kovalenko, M., et al. 1994. Cancer Res. 54, 6106),
- (v) 0.5 ml of a medium containing a preset concentration of cyproterone acetate and 20μ M SU4984 (Mohammadi, M., et al. 1997. Science 276, 955), were added, respectively.

After cultivation at 37°C in the presence of 5% CO₂ for 4 days, the number of cells in each well was determined using a CDA-500 (Table 1).

Results

Table 1

	Condition	Activity of Inhibiting Cell Growth (%)
(i)	5×10^{-6} M cyproterone acetate	20
(ii)	5×10^{-6} M cyproterone acetate + 0.2μ M AG17	40
(iii)	5×10^{-6} M cyproterone acetate + 10μ M AG1024	61
(iv)	5×10^{-6} M cyproterone acetate + 10μ M AG1296	42
(v)	5×10^{-6} M cyproterone acetate + 10μ M SU498475	75

The results show that a combination of cyproterone acetate and a tyrosine kinase inhibitor possesses an excellent activity of inhibiting a cell growth of a non-hormone dependent prostatic cancer cell more than cyproterone acetate.

I further declare that all statements made herein are of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Osaka, Japan this 22th day of November, 2005

A handwritten signature in cursive script, appearing to read 'Kenichiro Naito', is written over a horizontal line.

Kenichiro NAITO